How similar is similar? Exploring the binary and ternary solid solution landscapes of p-methyl/chloro/bromo-benzyl alcohols

How similar is similar? Exploring the binary and ternary solid solution landscapes of *p*-methyl/chloro/bromo-benzyl alcohols†

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New binary and ternary solid solutions formed by *p*-chlorobenzyl alcohol (*p*-ClBA), *p*-bromobenzyl alcohol (*p*-BrBA) and their quasi-isostructural compound *p*-methylbenzyl alcohol (*p*-MeBA) have been prepared and characterized by DSC and powder X-ray diffraction. The binary and ternary solid solutions were synthesized by co-melting of *p*-MeBA/*p*-ClBA, *p*-MeBA/*p*-BrBA and *p*-ClBA/*p*-BrBA and by co-melting of *p*-MeBA/*p*-ClBA/*p*-BrBA in various molar ratios. By varying the relative concentrations, it has been possible to observe the consequent variations of the melting points of the solid solutions. For the binary 1:1 *p*-MeBA/*p*-BrBA and *p*-ClBA/*p*-BrBA compounds, single crystals were grown from solution and their structures were investigated by X-ray diffraction.

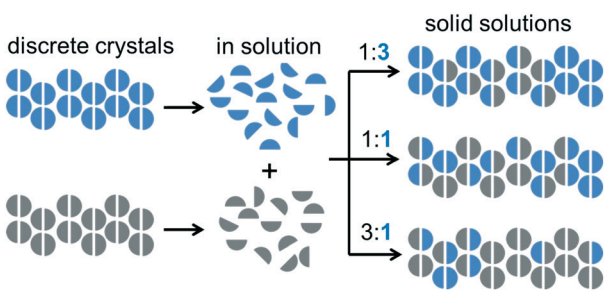
Multicomponent solids are attractive targets in the quest for novel specialized materials.[1] Crystal engineering[2] provides efficient tools to exploit the knowledge of crystal packing and of the forces acting between molecules to design new multicomponent materials with desirable structural and/or physico-chemical characteristics. The basic idea is that of being able to tune solid state properties such as melting point, hygroscopicity, solubility, stability, refractive index, thermal conductivity, surface activity, density, and electrostatic, mechanical and optical properties *via* a careful choice of molecular/ionic building blocks.[3] Clearly, the occurrence of polymorphism, *i.e.* the possibility of more than one result in the aggregation of the same molecules resulting in unforeseeable differences in solid state properties, needs also to be kept in mind.[4]

Co-crystals are stoichiometric multi-component crystalline materials formed by components that are solid under ambient conditions.[5] Co-crystallization has also proven to be a method to further explore, hence extend, the intellectual property right protection of active pharmaceutical ingredients (API) giving access to novel and/or improved properties provided that the API is co-crystallized with molecules[6] acceptable in the pharmacopoeia.[7]

More recently, the field has been expanded with the systematic preparation of ionic co-crystals,[8] where neutral organic molecules, including active pharmaceutical ingredients (APIs), are co-crystallized with an inorganic salt (typically halides of the first and second groups).

On the other hand, when multiple components combine in a single crystalline phase in nonstoichiometric ratios,[9] mixed crystals are formed with random occupancy of unit cell sites, which also currently find applications in the pharmaceutical field.[10] By not being limited to integral stoichiometry, a wide range of properties of the resulting solid can be controlled just by adding or decreasing the amount of a certain component.[11]

Clearly, miscibility of the components is the prerequisite for the formation of a solid solution. Miscibility depends very much on two related concepts, namely, structural mimicry[12] and crystal isomorphism. Two crystals are said to be



Scheme 1 Solid solutions formed by quasi-isostructural molecules crystallizing in isomorphous crystals.

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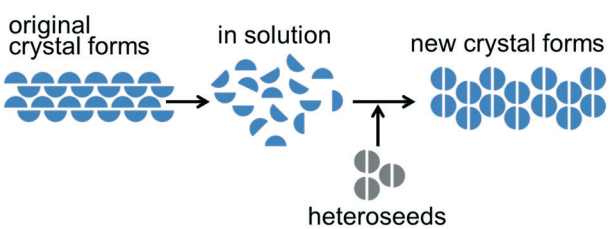
isomorphous if "(a) both have the same space group and unit-cell dimensions and (b) the types and the positions of atoms in both are the same except for a replacement of one or more atoms in one structure with different types of atoms in the other [...] or the presence of one or more additional atoms in one of them [...]. Isomorphous crystals can form *solid solutions*."[13] Molecules forming isomorphous crystals may crystallize together into a single lattice, randomly replacing one another within the crystal as represented schematically in Scheme 1. In the case of molecules that do not form isomorphous crystals, however, their quasi-isostructurality can still allow formation of multicomponent crystals, which are usually isomorphous with one of the two parent crystals.[14]

These principles can be illustrated by the chloro-methyl exchange,[15] which pertains to quasi-isostructural molecules differing by a chlorine group replacing a methyl group or *vice versa*. Methyl- and chloro- groups have been known to possess similar shape and size, with van der Waals volumes of *ca.* 19 Å^3 and 21 Å^3, respectively.[16] Taking this into account, it has been shown that it is possible for molecules with these groups in equivalent sites to be interchangeable in a crystal structure. In fact, a survey of the Cambridge Crystallographic Database has shown that approximately 30% of molecular pairs only differing by a methyl group replacing a chloro group crystallize with isostructural packing arrangements.[17] This scheme has been the basis for the preparation of new multicomponent crystals (Scheme 1).[18]

Following this approach,[19] we have reported, together with others, a structural and solid state NMR study of solid solutions of *para*-methylbenzyl alcohol (*p*-MeBA) and *para*-chlorobenzyl alcohol (*p*-ClBA).[14] In order to explore the solid solution space of *p*-MeBA and *p*-ClBA, isomorphous crystals of *p*-MeBa I were first prepared by seeding a solution of the known form II of *p*-MeBA with crystals of *p*-ClBA, by taking advantage of the large difference in solubility in hexane of the two species. The procedure used in that investigation is schematically represented in Scheme 2.

The *heteroseeding* procedure, therefore, also provides viable routes to the preparation of a desired solid form when it is possible to exploit shape mimicry. Jones *et al.*[19] reported that a solid solution can be obtained from the crystallization of chlorine cyclopentanone with the methyl derivative: through structural mimicry, the methyl derivative was induced to adopt molecular conformation, crystal structure and solid state reactivity of the chlorine analog.



Scheme 2 Schematic illustration of heteroseeding to generate a new polymorphic form of *p*-MeBA isomorphous with the crystals of *p*-ClBA.

A major drawback in the preparation of solid solutions of molecular crystals is that, for many systems, there is only a limited composition range wherein a homogenous phase is observed.[20] As interest in solid solutions of organic molecules has just started to develop, this is one of the many challenges that crystal engineers face in the synthesis of solid solutions with desired properties. For instance, in an attempt to circumvent this problem, a third component can be added to facilitate the mixing of two incompatible components. Anthracene and phenazine usually crystallize as separate phases; however, in the presence of acridine, which is miscible in both, a mixed crystal can be formed.[21]

In this study, we extend our approach to binary solid solutions of *p*-MeBA and *p*-ClBA with the bromine equivalent, *p*-BrBA, and also explore the preparation and thermal behaviour of three-component solid solutions consisting of the methyl-, chloro- and bromo-benzyl alcohols (see Scheme 3).

The mixed crystals have been investigated by a combined use of differential scanning calorimetry (DSC) and powder and single crystal diffraction measurements. The combined use of these methods has made possible a mapping of the solid-solution landscape and showed how the composition affects the melting temperature of the mixed systems with respect to the pure parent materials.

Experimental section

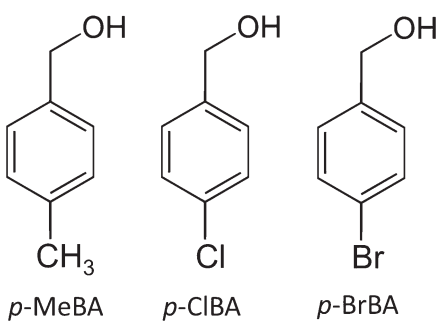
All reagents and solvents were purchased from Sigma-Aldrich and used without further purification.

Solid solutions by co-melting

To obtain binary and ternary solid solutions, *p*-MeBA, *p*-ClBA and *p*-BrBA were melted with stirring at the desired molar ratio. The melts were allowed to cool slowly to room temperature. The resulting powders were characterized by XRPD and DSC.

X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns were collected at room temperature using a PANalytical X'Pert PRO automated



Scheme 3 Formulae of the solid compounds used to prepare binary and ternary solid solutions: *p*-methylbenzyl alcohol (*p*-MeBA, form II), *p*-chlorobenzyl alcohol (*p*-ClBA), and *p*-bromobenzyl alcohol (*p*-BrBA).

diffractometer equipped with an X'celerator detector in the 2θ range of 3–50° (step size 0.011, time/step 50 s, $V \times A$ 40 × 40).

Differential scanning calorimetry

DSC measurements were carried out using a Perkin-Elmer Diamond equipped with a model ULSP90 intracooler. The samples (3–5 mg) were placed in aluminum open pans. Heating was carried out at 5 °C min^{-1}.

Crystal structure determination

Single crystals for X-ray diffraction were obtained by slow evaporation of EtOH solutions. Single crystal X-ray data for *p*-BrBA, *p*-$MeBA_{0.5}BrBA_{0.5}$ and *p*-$ClBA_{0.5}BrBA_{0.5}$ were collected at room temperature using an Oxford X'Calibur S CCD diffractometer equipped with a graphite monochromator (Mo-Kα radiation, λ = 0.71073 Å). Crystal data and details of the measurement are listed in Table S1.† The Me group and the Br atom in $MeBA_{0.5}BrBA_{0.5}$ and the Cl and Br atoms in *p*-$ClBA_{0.5}BrBA_{0.5}$ were treated as disordered 50 : 50 over two positions: the occupancy factor was first refined by keeping the isotropic thermal parameters fixed, then the occupancy factor was fixed and both C and Br or Cl and Br atoms were refined anisotropically. All non-hydrogen atoms were refined anisotropically; H atoms were added in calculated positions and refined riding on their respective carbon or oxygen atoms. In both mixed crystals, the phenyl rings were treated as rigid groups. SHELX97 (ref. 22*a*) was used for structure solution and refinement on F^2; Schakal99 (ref. 22*b*) was used for molecular graphics; Mercury[22c] was used to simulate powder patterns on the basis of single crystal data. The CCDC numbers are 1513379 (*p*-BrBA), 1513380 (*p*-$MeBA_{0.5}BrBA_{0.5}$) and 1513381 (*p*-$ClBA_{0.5}BrBA_{0.5}$).

Before proceeding with the discussion, a word of caution is in order. If taken separately, the results of single crystal X-ray diffraction, powder X-ray diffraction, and DSC measurements, in view of their complexity, are not sufficient *per se* to characterize the mixed systems with the desired degree of confidence. For instance, the existence of crystals of different compositions within the powder samples or the presence of block disorder in the single crystals cannot be entirely ruled out. It should be kept in mind that X-ray diffraction operates an average over space (and time, but this aspect is less relevant in the context of this paper), and that this average affects the sample in a different way in the case of single crystals than in the case of powder samples. Analogously, DSC results are affected by particle size distribution, sample homogeneity, and phase purity among other factors. It is only the concurrent output of these methods that provides a coherent picture.

Results and discussion

The crystal structures of *p*-MeBA, *p*-ClBA and *p*-BrBA have been studied extensively in the past. Here we only need to summarize some of the key aspects. The commercially available form of *p*-MeBA, form II, crystallizes in the monoclinic system $P2_1$ with three independent molecules in the asymmetric unit,[23] while *p*-ClBA contains only one independent molecule in the asymmetric unit.[24] Both *p*-ClBA and *p*-MeBA II show the presence of infinite hydrogen bonded chains in their solids. Form I of *p*-MeBA (XABREY06), isomorphous with *p*-ClBA, was previously synthesized by hetero-seeding a solution of form II with crystals of *p*-ClBA.[14] The hetero-seeding product *p*-MeBA I was found to be a metastable form that converted into the thermodynamically stable *p*-MeBA II in one week.[14] It is also interesting to note that this runs contrary to the hypothesis that the lower Z' in *p*-MeBA I (Z' = 1) should make it more stable than *p*-MeBA II (Z' = 3).[25] Only one form is known for *p*-BrBA, and it is isomorphous with *p*-ClBA.[26] Fig. 1 shows the main packing motif, with infinite chains of molecules connected *via* $OH\cdots O_{OH}$ hydrogen bonds, in *p*-MeBA, *p*-ClBA and *p*-BrBA.

Binary solid solutions: *p*-$MeBA_{1-x}BrBA_x$ and *p*-$ClBA_{1-x}BrBA_x$

The preparation of the solid solutions of *p*-$MeBA_{1-x}BrBA_x$ and *p*-$ClBA_{1-x}BrBA_x$ was based on co-melting, *viz.* on melting of the mixture of pure components, followed by slow cooling to room temperature. The solid mixtures were characterized by DSC and X-ray powder diffraction. In some cases, single crystals were grown from ethanol solutions in the presence of seeds. The results of the binary crystals will be compared also with reference to the binary solid solutions of *p*-MeBA and *p*-ClBA, previously reported.[14]

Since the *p*-BrBA molecule is isostructural with *p*-MeBA and *p*-ClBA and their crystals are isomorphous, it is can be expected that *p*-BrBA may be able to form binary solid solutions with either *p*-MeBA or *p*-ClBA. Melting together *p*-MeBA and *p*-BrBA in various stoichiometric ratios yields solid solutions, as confirmed by DSC and XRPD. The DSC of each product shows only one peak, pertaining to the formed solid solution and not to the reagents. The melting point trend in the phase diagram of *p*-$MeBA_{1-x}BrBA_x$ is analogous to the one observed for *p*-$MeBA_{1-x}ClBA_x$, with a pronounced minimum covering a fairly large compositional range, as shown in Fig. 2.

A comparison of the experimental X-ray powder diffraction patterns measured at room temperature on *p*-$MeBA_{1-x}BrBA_x$ solid solutions is shown in Fig. 3. It can be appreciated how the patterns progressively change between those of the isomorphous pure compounds in the $P2_1/c$ structures, reflecting the change in cell volume.

The solid solutions obtained *via* co-melting were in most cases recrystallized from solution, in order to attempt growth of single crystals for X-ray structural characterization. Only in the case of *p*-$MeBA_{0.5}BrBA_{0.5}$ we succeeded in growing single crystals for structural characterization.

Crystalline $MeBA_{0.5}BrBA_{0.5}$ is isomorphous with *p*-MeBA I and *p*-BrBA, and the methyl group and the bromine atoms show a 50% positional disorder, as shown in Fig. 4.

Analogous investigation was carried out on solid solutions of *p*-ClBA/*p*-BrBA. However, contrary to what was observed for

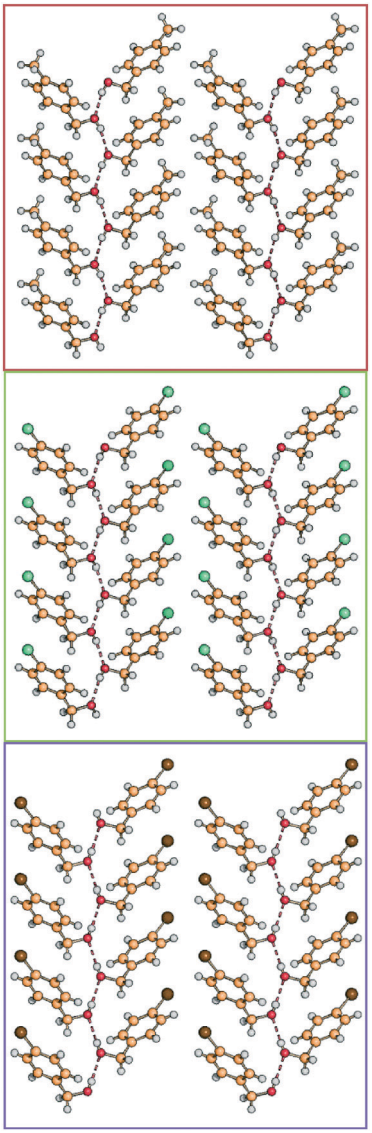


Fig. 1 Main packing motif, with hydrogen bonds involving the –OH groups in infinite chains, in isomorphous crystalline *p*-MeBA form I (XABREY06, top), *p*-ClBA (GAKNAH, middle) and *p*-BrBA (bottom).

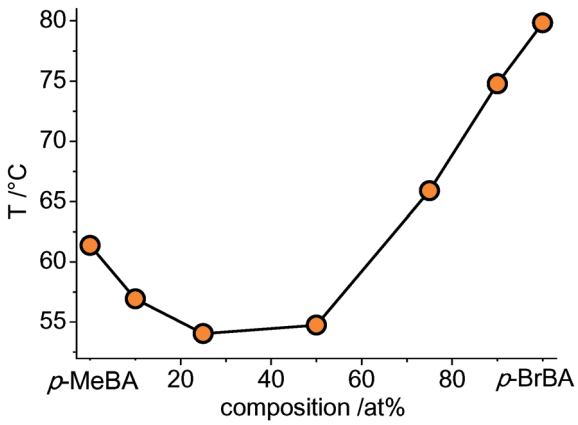


Fig. 2 Melting points (DSC *peak* temperatures) *vs.* atomic fraction of *p*-BrBA in *p*-$MeBA_{1-x}BrBA_x$ solid solutions.

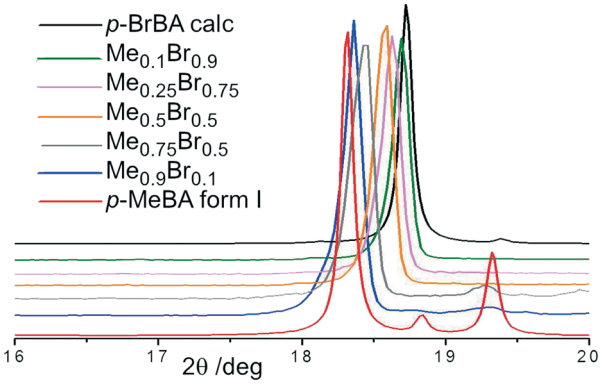


Fig. 3 Comparison of XRPD powder patterns for *p*-$MeBA_{1-x}BrBA_x$ solid solutions, showing a slight but consistent shift of the (−1 0 2) reflection towards higher 2θ angle on passing from the methyl derivative (bottom line) to the bromine derivative (upper line).

the mixtures containing *p*-MeBA, the melting points of the solid solutions are approximately all in between the values of the pure components (see Fig. 5).

A comparison of the experimental X-ray powder diffraction patterns measured at room temperature on *p*-$MeBA_{1-x}BrBA_x$ solid solutions is shown in Fig. 6. As observed for the *p*-$MeBA_{1-x}BrBA_x$ solid solutions, the patterns progressively, although not linearly, change between those of the isomorphous pure compounds in the $P2_1/c$ structures; for the sake of clarity, only the (−1 0 2) reflection (compare with Fig. 3) is been monitored here; a comparison of the XRPD patterns in the whole 2θ range is reported in the ESI.†

Single crystals for a detailed structural analysis could be grown from solution only in the case of *p*-$ClBA_{0.5}BrBA_{0.5}$ (see Fig. 7). Single crystals grown from a solution with Cl : Br in a 10 : 90 ratio turned out to be the pure *p*-BrBA compound, for which no room temperature data were available in the literature. A good quality structure was refined and structural details have been deposited in the CSD (see the ESI† and Fig. 1).

It is worth mentioning, on passing, that the unit cell parameters for the mixed systems are in between those for

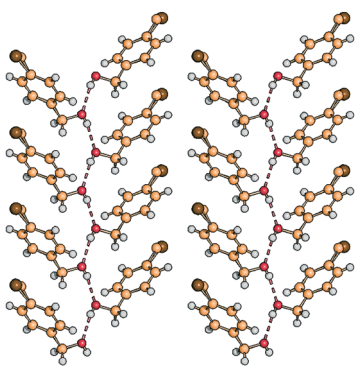


Fig. 4 Crystal packing of 50 : 50 *p*-MeBA/*p*-BrBA solid solution (projection in the *bc*-plane). Both images of disorder are shown for Me/Br (orange and brown spheres, respectively).

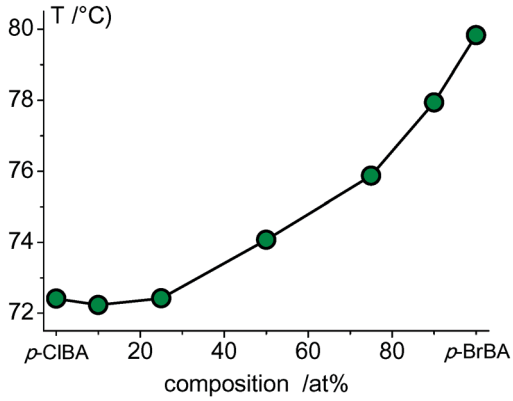


Fig. 5 Melting points (DSC peak temperatures) of the p-$ClBA_{1-x}BrBA_x$ solid solutions obtained by co-melting.

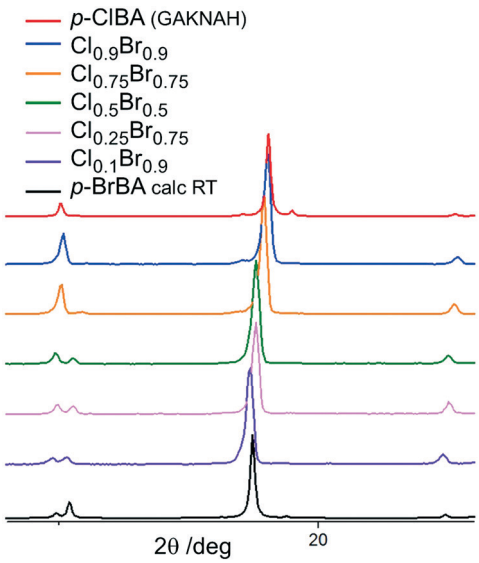


Fig. 6 Comparison of experimental X-ray powder patterns for p-$ClBA_{1-x}BrBA_x$ solid solutions, showing a slight average shift of the (−1 0 2) reflection towards higher 2θ angle on passing from the bromine derivative (bottom line, calculated pattern) to the chlorine derivative (upper line, calculated pattern).

the pure compounds, thus following the well-known Vegard's rule (see the ESI†).[27]

The behaviours with temperature of the three binary solid solutions obtained by co-melting are compared schematically in Fig. 8. All three pairs represent solid solution systems with complete miscibility. In the case of p-$ClBA_{1-x}BrBA_x$, the phase diagram is the simplest possible one, with the solidus line decreasing smoothly on decreasing amount of chlorine in the solution (see Fig. 8a)

Solid solutions with complete miscibility, however, can also exhibit a thermal minimum, as shown in Fig. 8b: this is the case of p-$MeBA_{1-x}ClBA_x$ (ref. 14) and p-$MeBA_{1-x}BrBA_x$, for which the melting points reach a minimum for x *ca.* 0.5 and x *ca.* 0.25, respectively. It is important to stress, however, that this minimum is an *indifferent point*, not a triple point, as only two phases (the solid solution and the liquid) exist in

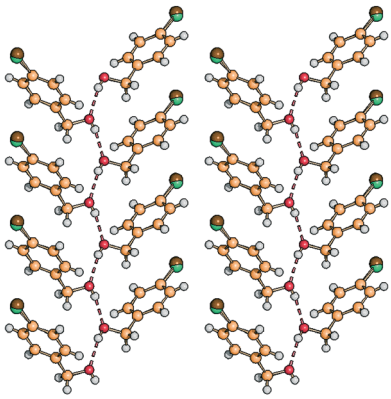


Fig. 7 Crystal packing of 50 : 50 p-ClBA/p-BrBA solid solution (projection in the bc-plane). Both images of disorder are shown for Cl/Br (green and brown spheres, respectively).

equilibrium, and the liquidus curve is tangential to the solidus curve (see inlet in Fig. 8, bottom).[26]

Ternary solid solutions: p-$MeBA_{1-x-y}ClBA_xBrBA_y$ solid solutions

As a natural extension of our study on two-component solid solutions of the three isomorphous solids p-MeBA, p-ClBA and p-BrBA, the propensity of these systems to form three-component solid solutions was also investigated. We

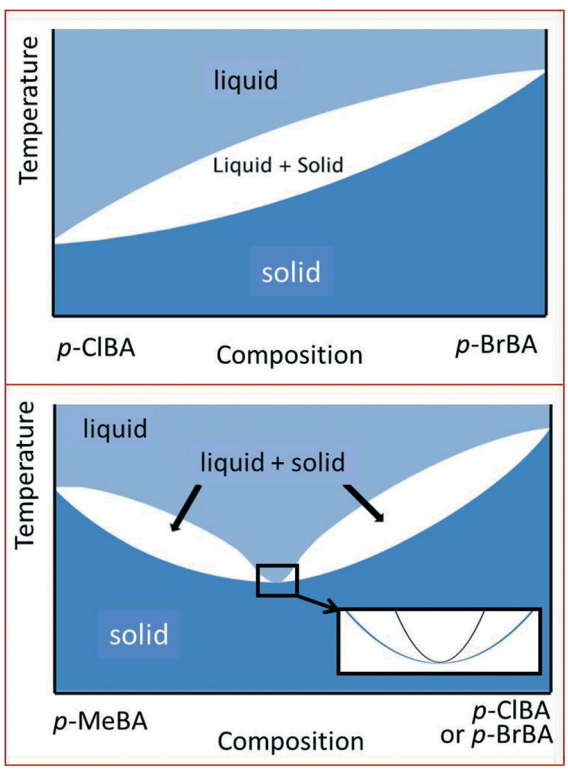


Fig. 8 Phase diagrams showing the two types of behaviours of the binary solid solutions: solid solutions of p-MeBA/p-ClBA and p-MeBA/p-BrBA show the "two lenses" behaviour (bottom), while those of p-ClBA/p-BrBA shows the "one lens" behaviour (top).

expected, however, increasing difficulties in the solid state characterization of the possible products, because of the higher complexity of the systems. The ternary 1 : 1 : 1 solid solution prepared, as in the case of the binary solid solutions, by co-melting showed distinct peaks in the XRPD pattern (Fig. 9), which could be attributed to the formation of the ternary phase, isomorphous with the parent ones. DSC measurements were instrumental in confirming the formation of the ternary solution, as only one peak was observed, at a different temperature with respect to the previously analysed solid solutions. Fig. 9 shows a comparison of the experimental pattern for the ternary 1 : 1 : 1 solid solution and the calculated patterns at room temperature for the pure parent compounds: the behaviour of the (−1 0 2) reflection is followed, as in Fig. 3 and 6 (a comparison over the whole 2θ range is reported in the ESI†).

Growing single crystals of the ternary solid solution, however, *via* dissolution in ethanol followed by slow evaporation, proved, up to now, to be a frustrating effort; all single crystals used for structural determination turned out to be either the pure chlorine derivative or crystals of low quality and difficult to refine.

Solid solutions of *p*-MeBA/*p*-ClBA/*p*-BrBA were also prepared at various stoichiometric ratios. DSC measurements of the solid solutions at various ratios revealed only one phase for each composition. Varying the concentration of one component while leaving the two other components to be equimolar resulted in slight changes in the corresponding XRPD patterns (see ESI†).

In order to investigate the melting point behavior of the ternary system, a large number of DSC measurements were carried out (see the ESI†). Fig. 10 provides a visual representation of the results. Generally, the melting points of the solid solutions were lower than those of the pure coformers; the lowest melting points for the ternary solid solutions were found at excess *p*-MeBA, with the *p*-$MeBA_{0.5y}ClBA_{0.25}BrBA_{0.25}$ solid solution showing the lowest one.

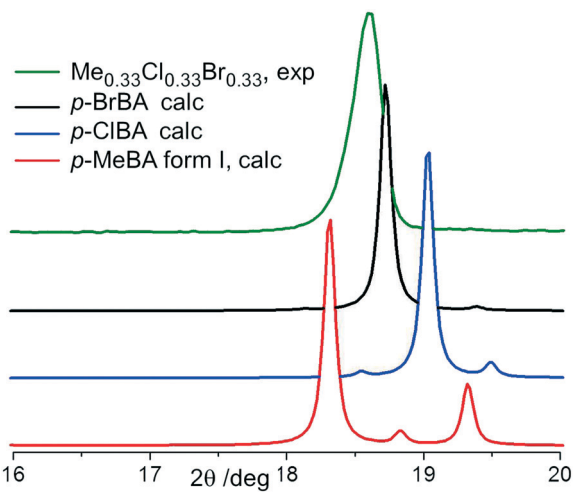


Fig. 9 Comparison between the experimental XRPD pattern for the *p*-$ClBA_{0.33}BrBA_{0.33}BrBA_{0.33}$ ternary solid solution (upper line) and the RT calculated ones (from top to bottom) of the pure bromine, chlorine and methyl derivatives, respectively, showing the relative angular shift of the (−1 0 2) reflection present in their isomorphous crystals [commercial forms II (BARBAC02) and I (THBARB), respectively].

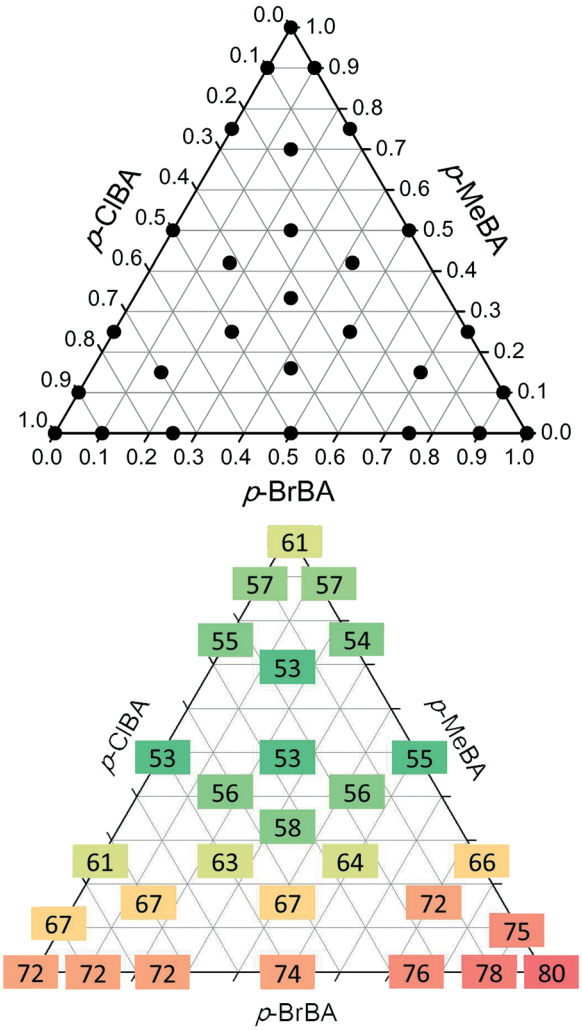


Fig. 10 Ternary diagrams showing (top) compositions of the *p*-$MeBA_{1-x-y}ClBA_xBrBA_y$ solid solutions as black dots and (bottom) the corresponding melting points (°C, peak temperatures from DSC). Red and green colours (yellow in between) mark high and low melting points, respectively.

Conclusions

In this paper we have extended our previous work[14] on solid solutions of *p*-MeBA and *p*-ClBA to the bromine analogue *p*-BrBA, obtaining new binary solid solutions from *p*-MeBA/*p*-BrBA and *p*-ClBA/*p*-BrBA. These crystalline materials demonstrated to be particularly well suited for this benchmarking study, permitting facile preparation by co-melting of the solid solutions, characterization by powder diffraction and isolation from solution of 50 : 50 products in the form of single crystals. The new mixed crystals were successfully synthesized with various molar ratios. In view of the quasi isostructurality

of the three compounds and of the fact that all compounds crystallize in isomorphous crystals, preparation of ternary solid solutions from *p*-MeBA/*p*-ClBA/*p*-BrBA has also been attempted and successfully carried out.

The study showed that the melting points of the solid solutions formed by molecular crystals synthesized changed according to the composition chosen for the preparation of the solid mixtures prior to co-melting. The three binary solid solutions showed two different types of trends with respect to the melting points. Solid solutions of *p*-MeBA/*p*-ClBA and *p*-MeBA/*p*-BrBA show minima at different compositions some 18 °C lower than that of the lowest melting substance, *e.g.* *p*-MeBa form II, while the *p*-ClBA/*p*-BrBA solid solutions melt at a temperature systematically lower than those obtained by linear averaging but comprised between the melting points of the two pure components. The ternary *p*-MeBA/*p*-ClBA/*p*-BrBA solutions also show isomorphicity with the $P2_1/c$ parent structures, while the melting points are systematically lower than those obtained by weighted average of the components.

It is interesting to note that in the presence of polymorphic modifications, the metastable form of *p*-MeBA is preferred, showing the "adaptive capacity" of the packing of *p*-MeBA when mixed with *p*-ClBA and *p*-BrBA.

Having been successful with these model molecules, research will proceed with more complex molecules, in order to understand to which extent the ternary replacement is exploitable. Our aim is to extend our approach to systems where properties can be adapted to the target by a change in solid solution composition.

Acknowledgements

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